**Section III. REMARKS**

The pending claims in the application are 1, 3-10, 12-19, 21-28, 31-32, 62-72, 74-76 and 78-82. Claims 62-65 have been withdrawn, subject to rejoinder (see below).

**Rejoinder of Claims 62-65 Upon Finding of Allowable Group I Product Claim(s)**

In the February 21, 2003 Office Action, the Examiner has acknowledged applicant's request for rejoinder of Group III and Group IV claims under the provisions of MPEP §821.04, and stated that upon finding product claim(s) of Group I allowable, the Group III and IV claims "previously withdrawn from consideration as a result of a restriction requirement, will be rejoined and fully examined for patentability under 37 CFR 1.104" (see February 21, 2003 Office Action, page 2, second paragraph).

In connection with such prospective rejoinder, applicant has added new method claims 82-85 to cover biocatalysis applications of the invention using enzyme-fusion proteins including an ELP, for inclusion in the rejoined claims.

The new claims 82-85 are consistent with and supported by the disclosure at page 21, lines 21-26 of the instant application.

**Objection to the Drawing (FIG. 3)**

In response to the Examiner's objection to Figure 3 as previously submitted, a new drawing sheet containing FIGS. 2 and 3 is enclosed in Appendix A hereof. In the new sheet of drawings, the spelling of the term "TENDAMISTAT" has been corrected.

The new drawing sheet fully complies with the requirements of 37 CFR §1.84.

It therefore is requested that the new sheet of drawings for FIGS. 2 and 3 be entered in substitution of the corresponding sheet of drawings previously submitted in the application.

**Rejection of Claims and Traversal Thereof**

In the February 21, 2003 Office Action:

claims 1-8, 17-20, 25-26, 31, 33, 71-72 and 76-77 were rejected under 35 U.S.C. §112, second paragraph as indefinite for failing to particularly point out and distinctly claim the invention;

claims 1, 3-10, 12-19, 27-28, 31-32, 66-72 and 74-76 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification;

claims 1, 4, 6, 21, 25, 26, 27, 28 and 31 were rejected under 35 U.S.C. §102 (b) as being anticipated by McPherson et al. (D.T. McPherson, C. Morrow, D.S. Minehan, J. Xu, E. Hunter, D.W. Urry, "Production and Purification of a Recombinant Elastomeric Polypeptide G-$(VPGVG)_{19}$-VPGV, from *Escherichia coli*," *Biotechnol. Prog.*, 8, 347-352 (1992)).

These various rejections are traversed. Reconsideration of the patentability of the claims, as amended herein, is requested in light of the ensuing remarks.

**Rejections under 35 U.S.C. §112, second paragraph**

In the February 21, 2003 Office Action, claims 1-8, 17-19, 25, 26, 31, 71, 72, 76 and 77 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has raised numerous grounds for such §112, second paragraph rejection.

Each of such grounds is addressed in turn below.

(1) Claims 1-7, 20, 25, 26, 31 and 33 were rejected under §112, second paragraph, as being indefinite on the basis that they recite as part (b) "one or more phase transition proteins that exhibit an inverse phase transition" while "part (b) as disclosed in the specification comprises a peptide or a protein," which the Examiner has characterized as confusing (see February 21, 2003 Office Action, page 3, lines 9-18).

Applicants vigorously disagree.

Claims 2, 20 and 33 were previously cancelled in the Response to the November 18, 2002 Office Action, filed December 4, 2002. Accordingly, the rejection of these claims is moot.

According to Section 2173.01 of the MPEP, "[a] fundamental principle contained in 35 U.S.C. §112, second paragraph is that applicants are their own lexicographers." Further, MPEP §2173.05(a) states that:

> "When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art."

(citing *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989)). Accordingly, applicant is permitted to define claim terminology in the specification, provided the term is not given a meaning repugnant to the usual meaning of the term.[2]

In the present case, applicant has defined the term "protein" in his disclosure as follows:

> **"The term 'protein' is used herein in a generic sense to include polypeptides of any length."**

(specification, page 9, line 7). The definition of protein provided by applicant is not repugnant to the usual meaning of the word since **a protein is a polypeptide chain**. As such, applicant intended **the term "protein" to broadly cover polypeptide chains of any length including those consisting of 5-100 amino acids** and the claims must therefore be examined in light of this meaning.

(2) Claim 8 was rejected under §112, second paragraph because of the recital of the limitation "biological molecule of interest" in the second line. According to the Examiner, there is insufficient antecedent basis for this limitation in the claim.

In response, claim 8 has been amended to recite:

> **"The fusion protein of claim 7 wherein the antibody or antibody fragment has complex forming affinity for an antigenic protein of interest, and wherein upon binding to the antigenic protein of interest, the fusion protein retains some or all of its phase transition character."**

The specification discloses the binding of an antibody or antibody fragment to "a protein of interest" (see specification, page 5, line 27 to page 6, line 2), thereby forming a fusion protein comprising (i) the antibody of claim 7 (which is the biological molecule of claim (1)(a)), (ii) the phase transition protein of

[2] See, *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947).

claim (1)(b) **and** (iii) an additional "protein of interest" that binds to the antibody.

It is well known in the art that antibodies have specific binding affinity for the antigenic proteins that elicit or induce their synthesis.[3] Accordingly, it is evident within the skill of the art that "a protein of interest," as recited in newly amended claim 8, in the context of the applicant's disclosure, is an antigenic protein.

The terms in amended claim 8 therefore have proper antecedent basis and fully comport with the requirements of 35 U.S.C. §112, second paragraph.

(3) Claims 17-19 were rejected under 35 U.S.C. §112, second paragraph on the basis that (a) the abbreviation ELP should be expanded when used for the first time, and (b) the term ELP is confusing because of its dual meaning (see February 21, 2003 Office Action, page 4, lines 3-10).

In response, claims 17-19 have been amended herein to recite "phase transition protein(s) of 1(b)" in place of "ELP," for consistency of claims 17-19 with claim 12.

(4) Claim 71 was rejected under 35 U.S.C. §112, second paragraph on the basis that the term "composition conditions" and the phrase "predetermined change of composition conditions" were indefinite. In response, applicant has amended claim 71 to more clearly define the conditions that may be altered in order to effectuate a phase transition of the fusion protein.

Specifically, claim 71 as now amended recites, *inter alia*, "wherein the phase transition is mediated by at least one change selected from the group consisting of: (a) changing temperature; (b) changing pH; (c) addition of solutes and/or solvents; (d) side-chain ionization or chemical modification; and (e) changing pressure."

Claim 71 as amended is fully clear and definite.

(5) Claim 72 was rejected under 35 U.S.C. §112, second paragraph as lacking antecedent basis for the limitation "comprising a protein of interest cleavable from the ELP at a cleavage site of the ELP fusion protein," because claim 71 does not recite any protein of interest or a cleavage site. Claims 71 and 72 have been amended herein, thereby obviating this rejection.

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[3] See, *Biochemistry*, L. Stryer, W.H. Freeman and Co., New York, 3rd edition, page 62, 1988.

Specifically, claim 71 has been amended to recite an "elastin-like peptide fusion protein comprising a protein of interest and an ELP component coupled by a cleavage site," and claim 72 has been amended in conformity therewith.

(6) Claim 76 was rejected under 35 U.S.C. §112, second paragraph as not further limiting the claim from which it depends. Specifically, the Examiner stated:

> "[c]laim 76 recites the phase transition protein(s) comprising a β-turn structure. Claim 76 depends on claim 12 that recites the phase transition protein(s) comprising oligomeric repeats of pentapeptide Val-Pro-Gly-X-Gly. By definition, page 13, line 15 of the specification, these oligomeric repeats comprise a β-turn structure." [4]

Applicant vigorously disagrees.

At page 13, line 15, the instant application discloses that:

> **"[t]he phase transition component of the FP may comprise a β-turn component."**

In addition, at page 6, lines 7-8 of the instant specification, it is disclosed that:

> **"[t]he FPs of the invention comprise one or more proteins exhibiting a phase transition. These proteins preferably exhibit a β-turn structure, though such a structure is not strictly necessary."**

Considered **as a whole**, the disclosure in the instant application indicates that the FP **may comprise, but need not necessarily include,** a β-turn component.

The Examiner's contention that the oligomeric repeats **are required** to comprise a β-turn component is therefore incorrect.

Since the invention described in the specification must be considered as a whole, and since applicant explicitly teaches that the β-turn may, but need not necessarily, be present, thereby encompassing a contrary possibility of absence ("may" including the correlative possibility that the specified entity may NOT be present), there is no infirmity in claim 76.

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[4] See February 21, 2003 Office Action, page 5, first paragraph.

Claim 76 further limits claim 12 from which it depends.

(7) Claim 77 was rejected under 35 U.S.C. §112, second paragraph as depending from cancelled claim 35. Claim 77 has now been cancelled herein, thereby obviating such rejection.

In light of the foregoing, applicant respectfully requests withdrawal of the various §112, second paragraph rejections of claims 1-8, 17-19, 25, 26, 31, 71, 72, 76 and 77.

**Rejection under 35 U.S.C. §112, first paragraph**

In the February 21, 2003 Office Action, claims 1, 3-10, 12, 13-19, 27, 28, 31, 32, 66-72 and 74-76 were rejected under 35 U.S.C. §112, first paragraph on the basis that it contained subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant traverses this rejection and requests reconsideration of claims 1, 3-10, 12, 13-19, 27, 28, 31, 32, 66-72 and 74-76, as amended, in light of the following remarks.

(1) Claims 1, 3-10, 12, 13-19, 27-28, 31-32 and 76 were rejected under 35 U.S.C. §112, first paragraph, on the basis of written description. According to the Examiner, "the claims are directed to [a] large and variable genus of fusion proteins exhibiting a phase transition," however, the specification "is not sufficient for identifying the features of all proteins that are able to support the capacity of exhibiting the phase transition" (see February 21, 2003 Office Action, page 5, lines 16-20 to page 6, lines1-6).

Applicant vigorously disagrees.

The written description requirement is satisfied if a patent specification describes the claimed invention in sufficient detail so that one skilled in the art may reasonably conclude that the inventor had possession of the claimed invention as of the filing date sought.[5] For a claimed genus, the written description requirement may be satisfied if a "representative number of species" are sufficiently described by disclosure of relevant, identifying characteristics, such as physical or chemical properties,

[5] See MPEP §2163(I) (citing *Vas-Cath,Inc. v. Mahurkar*, 935 F.2d 19 USPQ2d 1111 (Fed. Cir. 1991)).

or functional characteristics.[6] Moreover, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[7]

Applicant has amended independent claims 1, 27 and 31, to include the limitation:

> **"wherein the fusion protein retains the inverse phase transition behavior of the phase transition proteins of (b)"**

Thus the presently claimed invention includes only those fusion proteins **that retain the inverse phase transition behavior of the phase transition proteins of (b)**.

In other words, using the Examiner's example, if one were to attach a protein (part (a)), having a molecular weight greater than 100 kDa and a large positive charge, to the appropriate phase transition proteins of part (b) and the fusion protein did retain the inverse phase transition behavior of the phase transition proteins of (b), it would be covered by claim 1 of the present invention.

Moreover, one of skill in the art would reasonably conclude that applicant had possession of amended claim 1 (and amended claim 27 and 31) as of the filing date. Applicant submits that regardless of the molecular weight of the biological molecule of (a), the skilled artisan will be able to effectively produce fusion proteins and subsequently purify them, as long as the fusion protein retains the inverse phase transition behavior of the phase transition proteins of (b).

As amply demonstrated by applicant, the molecular weight of the phase transition protein of (b) can be varied relative to the molecular weight of the biological molecule of (a), to causing variation in the transition temperature (see the instant specification, at page 45-51, section 6.8.11). For example, applicant discovered that the transition temperature ($T_t$) of the higher molecular weight FP constructs approached 40°C ($T_t$ = 42 °C for the thioredoxin-ELP[$V_5A_2G_3$-180], with $MW_{ELP}$ = 71 kDa, in PBS at 25 μM), while the $T_t$ of the lower molecular weight FP increased dramatically to nearly 80°C ($T_t$ = 77 °C for thioredoxin-ELP[$V_5A_2G_3$-30], with $MW_{ELP}$ = 13 kDa, under the same conditions) (see the instant specification, at page 46, lines 6-10).

Applicant's specification also discloses that green fluorescent protein (GFP) and blue fluorescent

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[6] See MPEP §2163(II)(A)(3)(a)(ii); Revised Interim Written Description Guidelines Training Materials, page 8, available at www.uspto.gov/web/patents/guides.htm.

[7] See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

protein (BFP) ELP fusion proteins were synthesized and were found to exhibit an inverse phase transition as a function of temperature (see disclosure, page 32, lines 9-15). GFP and BFP weigh 26.9 kDa and 25.8 kDa, respectively. Moreover, as stated in the disclosure, the GFP-ELP and the BFP-ELP both exhibited the inverse phase transition with both the ELP 90-mer (≈36 kDa) and ELP 180-mer (≈72 kDa). In sum, the molecular weight of the biological molecule of (a) is just another parameter that must be considered when designing fusion proteins for effective ITC purification.

Of more significant concern to the applicant was the physico-chemical and expression properties of the biological molecules of (a). Towards that end, proteins with extremely different expression and physico-chemical properties were specifically selected to demonstrate that regardless of the properties of the biological molecule of (a), fusion proteins could be produced and thereafter purified using the ITC method. As specifically disclosed in the instant application, thioredoxin, an over-expressed, highly soluble protein, as well as tendamistat, an under-expressed, insoluble peptide, were successfully fused to phase transition proteins that exhibit an inverse phase transition and thereafter purified using the ITC method.

Additionally, the specification discloses other examples of proteins that may be suitable fusion protein components, including:[8]

> **"enzymes utilized in replacement therapy; hormones for promoting growth in animals, or cell growth in cell culture; and active proteinaceous substances used in various applications, e.g., in biotechnology or in medical diagnostics. Specific examples include superoxide dismutase, interferon, asparaginease, glutamase, arginase, arginine deaminase, adenosine deaminase ribonuclease, trypsin, chromotrypsin, papin, insulin, calcitonin, ACTH, glucagon, somatosin, somatropin, somatomedin, parathyroid hormone, erthyropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, and vasopressin."**

The Examiner is reminded that description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.[9]

When considered against the requisite criteria for written description, as set out in the MPEP provisions and judicial decisions cited hereinabove, it is clear that the Applicant has disclosed ample description and examples to show that applicant was in possession of the invention as recited in amended claims 1,

[8] See disclosure, page 16, lines 25-30 to page 17, lines 1-2.
[9] See MPEP §2163(II)(A)(3)(a)(ii).

3-10, 12, 13-19, 27-28, 31-32 and 76. Applicant therefore requests withdrawal of the corresponding §112, first paragraph rejection of claims 1, 3-10, 12-19, 27-28, 31-32 and 76.

(2) Claims 1, 3-10, 27-28, and 31-32 were also rejected under 35 U.S.C. §112, first paragraph, as not setting forth the sequences of the phase transition protein (b) that are to be used for constructing the fusion protein, the Examiner contending that same showed that applicant was not in possession of the claimed invention at the time the application was filed.

Applicant vigorously disagrees.

To establish a *prima facie* case of unpatentability based on written description, the Examiner has the initial burden of providing reasons why a person skilled in the art, at the time the application was filed, would not recognize that the inventor was in possession of the claimed invention as claimed, in view of the disclosure of the application. See MPEP §2163.04.

Applicant submits that the Examiner has not satisfied this burden.

The art of phase transition proteins exhibiting an inverse phase transition was well known at the time the present application was filed, and is adequately disclosed in the specification (see disclosure, page 13, lines 17-20 and page 14, page 13-14). At pages 13-14 of the instant disclosure, applicant describes the use of the VPGXG pentapeptide, as well as the IPGXG pentapeptide. Additionally, applicant directs the reader of the instant application to International Patent Application PCT/US96/05186[10] for examples of additional suitable phase transition polypeptides, and such international patent application further directs the reader to U.S. Patent. Nos. 4,783,523, 4,870,055, 4,898,926, and U.S. Serial No.08/246,874, now U.S. Patent No. 5,527,610. Each of these references thoroughly describes elastin-like polypeptides that exhibit an inverse phase transition.

It would be within the ability of one skilled in the art, given the high level of knowledge and expertise in the general field of the instant invention, and the guidance and direction of the instant application, to prepare fusion proteins comprising elastin-like polypeptides (ELPs), using ELPs that were known and available at the time of filing the present invention, including those ELPs described in International Patent Application PCT/US96/05186 and U.S. Patent. Nos. 4,783,523, 4,870,055, 4,898,926, and U.S.

[10] See WO96/32406, published October 17, 1996, to Urry et al., claiming priority to U.S. Serial No. 08/543,020, now U.S. Patent No. 5,854,387.

Serial No.08/246,874, now U.S. Patent No. 5,527,610.

It again is emphasized that **what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail**.[11]

Withdrawal of the written description rejection of claims 1, 3-10, 27-28 and 31-32 therefore is merited, and is respectfully requested.

(3) Claims 71-72 and 74-75 were rejected under 35 U.S.C. §112, first paragraph, on the basis of written description, the Examiner contending that applicant had not described enough fusion proteins to encompass the scope of claim 71 and claims dependent therefrom.

Applicant disagrees.

It is to be noted that claim 71 recites an ELP fusion protein that must exhibit an inverse phase transition. Thus, the claimed "fusion protein" must exhibit an inverse phase transition - this requirement eliminates any fusion proteins that do not exhibit such behavior.

Further, the Examiner's attention is directed to the discussion in the preceding section, concerning the elastin-like polypeptides that exhibit an inverse phase transition, which were known at the time of filing of the instant application, and the disclosures in International Patent Application PCT/US96/05186 and U.S. Patent. Nos. 4,783,523, 4,870,055, 4,898,926, and U.S. Serial No.08/246,874, now U.S. Patent No. 5,527,610, relating to such ELP species.

It would be within the ability of one skilled in the art, given the high level of knowledge and expertise in the general field of the instant invention, and the guidance and direction of the instant application, to prepare the claimed fusion proteins comprising elastin-like polypeptides (ELPs), using ELPs that were known and available at the time of filing the present invention.

Applicant therefore respectfully requests withdrawal of the written description rejection of claims 71-72 and 74-75.

(4) Claims 9 and 66-70 were rejected under 35 U.S.C. §112, first paragraph, on the basis of written

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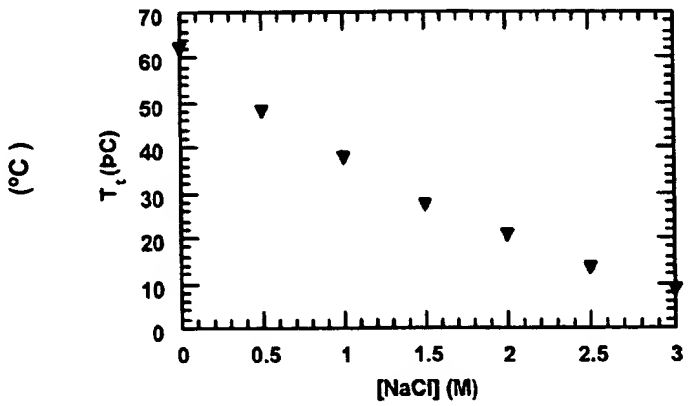
[11] See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 at 1384, 231 at 94.

description, the Examiner contending that neither the claim nor the specification describes the phase transition of the claimed fusion protein "wherein the phase transition is mediated by changing pH, addition of solutes and/or solvents, side chain ionization, chemical modification, and changing pressure" (see February 21, 2003 Office Action, page 8, lines 6-14).

Applicant vigorously disagrees.

The Examiner concedes that the disclosure sets forth the phase transition induced by changes of temperature. Applicant points out that the disclosure also describes the phase transition induced by the presence of solutes and that one of skill in the art would know that the mediation of other physical-chemical conditions would also induce phase transition, as discussed below.

Referring to the applicant's specification, the phase transition induced by the presence of solutes is expressly disclosed wherein the solute is NaCl (see for example applicant's disclosure, page 15, lines 18-19, page 21, lines 7-11, page 37, lines 8-20, page 38, lines 11-25 and Figure 6). By way of specific example, Figure 6, as recreated below, represents a plot of transition temperature as a function of NaCl molar concentration for the thioredoxin/60-mer FP (25 μM) in 50 mM phosphate buffer at pH 8.0.




It can be seen that the transition temperature decreases with an increase in NaCl molarity. As such, one can perform the ITC process of the present invention by maintaining a constant temperature (i.e.,

maintenance of isothermal conditions) while simultaneously altering the solute concentration.

Additionally, applicant submits that one of skill in the art would know that the mediation of other conditions would also induce the ITC phase transition. For instance, the Urry reference AI[12] in the IDS submitted by applicant on June 29, 2001 thoroughly describes the mediation of the transition temperature of a phase transition protein.

By way of example, the phase transition can be mediated by a change in pH, as described on page 36 of the Urry AI reference. In that example, the $T_t$ of the phase transition corresponded to 24°C and 69°C at a pH of 3 and 7, respectively (see also Urry AI reference, Figure 14, page 39). As such, once the appropriate experimental conditions are determined, one can perform the ITC process of the present invention by maintaining a constant temperature while simultaneously varying the pH. Moreover, because many amino acids are sensitive to pH change, one of skill in the art would inherently understand that a change in pH, which may concomitantly induce side-chain ionization (where applicable), would cause a change in the $T_t$ of the phase transition.

In addition to the use of solutes, which applicant thoroughly described in the present specification, the use of solvents to alter the $T_t$ is also known in the art. Referring to the Urry AI reference, page 37, the use of ethylene glycol, dimethyl sulfoxide and urea as a $T_t$ mediator was disclosed. When the phase transition protein comprises certain aromatic residues such as Trp, Phe, and Tyr, an increase in external pressure raises the $T_t$ (see Urry AI reference, page 37).

In sum, applicant adequately described the use of solutes in the present specification and one of skill in the art would know that the mediation of pH, pressure or solvent concentration is also effective to cause a phase transition of the fusion protein.

Applicant therefore respectfully requests reconsideration and withdrawal of the rejection of claims 9 and 66-70 under 35 U.S.C. §112, first paragraph.

**Rejection under 35 U.S.C. §102**

In the February 21, 2003 Office Action, claims 1, 4, 6, 21, 25-28 and 31 were rejected under 35 U.S.C.

[12] D.W. Urry, Free Energy Transduction in Polypeptides and Proteins Based on Inverse Temperature Transitions, *Prog. Biophys. Molec. Biol.*, Vol. 57, pp 23-57, 1992.

§102(b) as being anticipated by McPherson et al.[13] (hereinafter McPherson). The Examiner contended that McPherson and co-workers teach the fusion protein having characteristics as claimed by applicant in claims 1, 4, 6, 21, 25-28 and 31.

Applicant traverses this rejection and respectfully points out that amended independent claims 1, 27 and 31, and the claims that depend therefrom, are not in any way anticipated by McPherson.

McPherson teaches the recombinant production and subsequent purification of the elastomeric polypeptide G-(VPGVG)$_{19}$-VPGV. More specifically, McPherson teaches that G-(VPGVG)$_{19}$-VPGV may be subcloned into pGEX-3X to create a gene that expresses G-(VPGVG)$_{19}$-VPGV as a C-terminal fusion to glutathione S-transferase (gst), with an Ile-Glu-Gly-Arg spacer located therebetween.[14] Following expression, the gst-G-(VPGVG)$_{19}$-VPGV fusion is affinity purified by glutathione-agarose. Thereafter, protease factor Xa[15] is added to cleave the gst from the G-(VPGVG)$_{19}$-VPGV at the Ile-Glu-Gly-Arg spacer and the G-(VPGVG)$_{19}$-VPGV is separated from the gst using glutathione-agarose affinity adsorption.

McPherson does not discuss or suggest that the gst-G-(VPGVG)$_{19}$-VPGV fusion protein retains the inverse phase transition behavior of the G-(VPGVG)$_{19}$-VPGV elastomeric compound, as recited in the presently amended claims.

Applicant has amended claim 1 to recite that the fusion protein, when present in the desolvated, insoluble phase, is of sufficient mass to be centrifugably removed from solution. Support for this terminology can be found in the disclosure at page 3, lines 27-30, page 4, lines 2-4 and page 16, lines 18-20 of the instant application. McPherson does not discuss or suggest that the gst-G-(VPGVG)$_{19}$-VPGV fusion will form aggregates of sufficient mass to be centrifugably removed from the solution. Thus, McPherson does not anticipate independent claim 1 or the claims depending therefrom.

Independent claim 27 has been amended to recite that the phase transition temperature of the fusion protein occurs in the range from about 35°C to about 60°C. Support for this amendment

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[13] D.T. McPherson, C. Morrow, D.S. Minehan, J. Xu, E. Hunter, D.W. Urry, "Production and Purification of a Recombinant Elastomeric Polypeptide G-(VPGVG)$_{19}$-VPGV, from *Escherichia coli*," *Biotechnol. Prog.*, 8, 347-352 (1992).

[14] See McPherson, page 349, Figure 2.

[15] Protease factor Xa is a serine protease.

can be found in the disclosure on page 15, lines 11-12. McPherson does not discuss or suggest that the gst-G-$(VPGVG)_{19}$-VPGV fusion will undergo a phase transition in the range from about 35°C to about 60°C. Thus, McPherson does not anticipate claim 27 or the claims depending therefrom.

Independent claim 31 was amended to include the proviso "that when the biological molecule of (a) is glutathione S-transferase and the spacer sequence of (c) is proteolytically cleavable, the spacer sequence of (c) is cleavable by a protease agent selected from the group consisting of cysteine, aspartyl and metallo-proteases." Support for this terminology can be found in the disclosure on page 18, lines 9-11. With the inclusion of the proviso, McPherson no longer anticipates claim 31.

Claims 1, 4, 6, 21, 25-28 and 31 as amended therefore are not anticipated by McPherson, and withdrawal of the rejection of such claims under 35 U.S.C. §102(b) is correspondingly respectfully requested.

**Fees Payable**

Applicant has added four (4) additional independent and four (4) additional dependent composition claims, however, since claim 77 has been cancelled herein, there is a net addition of seven (7) total claims, four (4) of which are independent, beyond the number for which payment previously has been submitted.

Accordingly, a check payable to Commissioner for Patents in the amount for $282.00 is enclosed herewith, to cover the added claims fee of $227 and the extension of time fee of $55.00 (see following section hereof).

Authorization hereby is given to charge any additional fee or amount necessary to the entry of this Amendment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**Section IV. Request for One Month Extension of Time**

Applicant hereby requests a one (1) month extension of time for reply to the February 21, 2003 Office Action. This request is made under the provisions of 37 CFR §1.136. The fee of $55.00

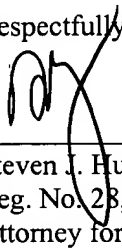
specified in 37 CFR §1.17 for such extension request is enclosed in the form of a check payable to Commissioner for Patents in the amount of $282.00 to cover the extension fee of $55 and the added claims fee of $227.00 (see preceding section hereof).

Authorization hereby is given to charge any additional fee or amount necessary to the entry of this Amendment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**Section V. CONCLUSION**

Based on the amendments made herein and the foregoing remarks, claims 1, 3-10, 12-19, 21-28, 31-32, 62-72, 74-76 and 78-82 are now in form and condition for allowance. The Examiner therefore is respectfully requested to reconsider and allow such amended claims.

Respectfully submitted,



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# APPENDIX A

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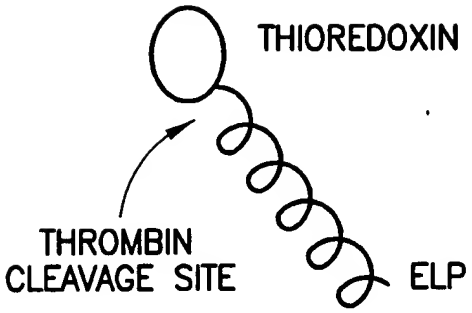


FIG.2

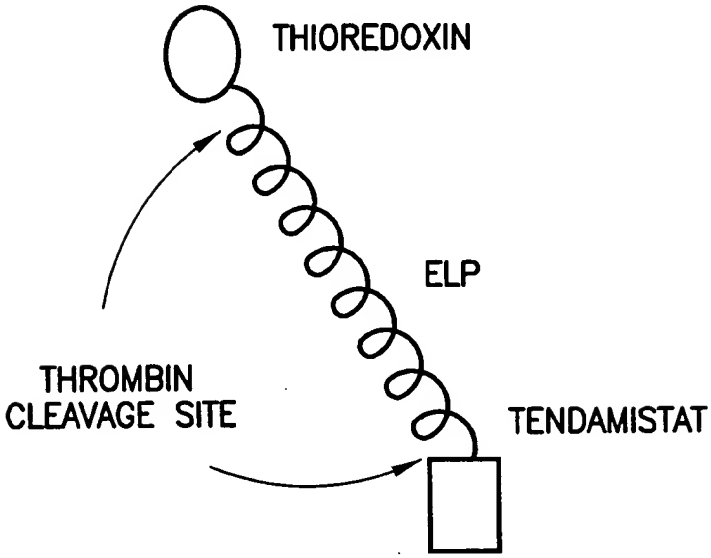


FIG.3